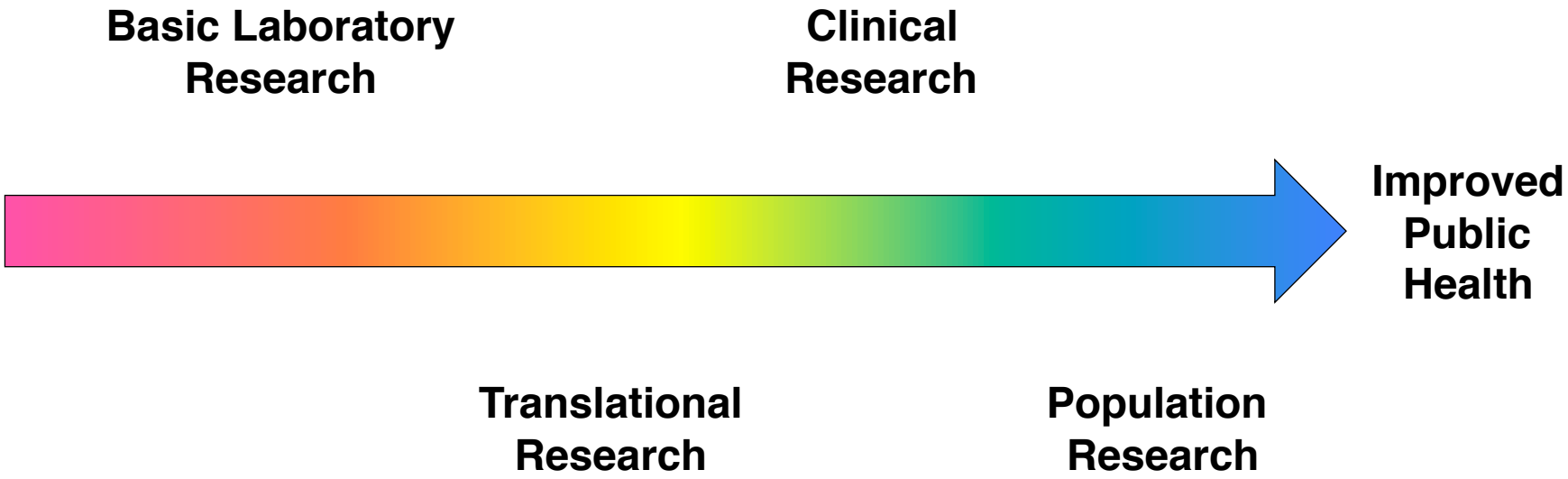
NCATS: Catalyzing Translational Innovation

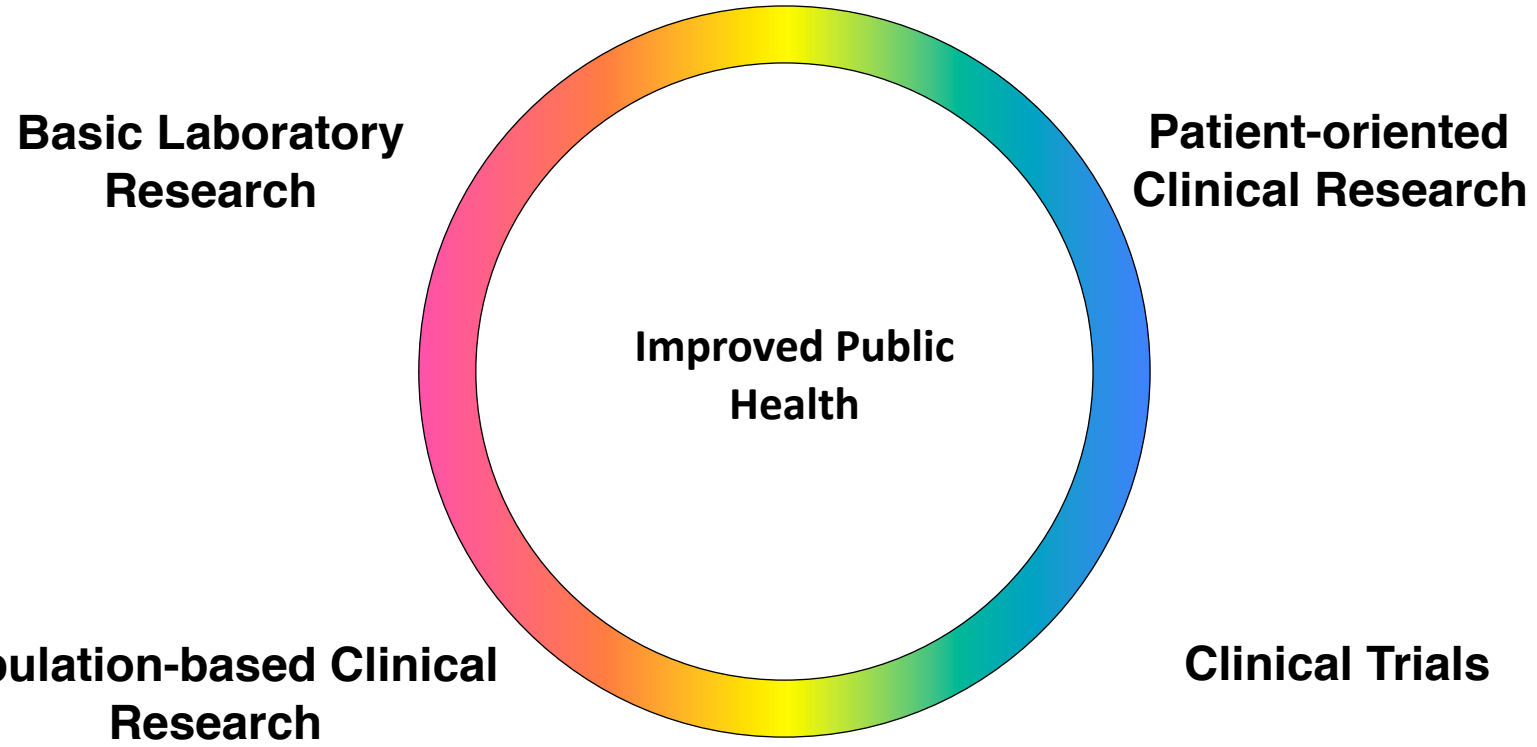
CHRISTOPHER P. AUSTIN, M.D.
NCATS DIRECTOR
FEBRUARY 5, 2013

NCATS

Standard Model



The Way It Should Work

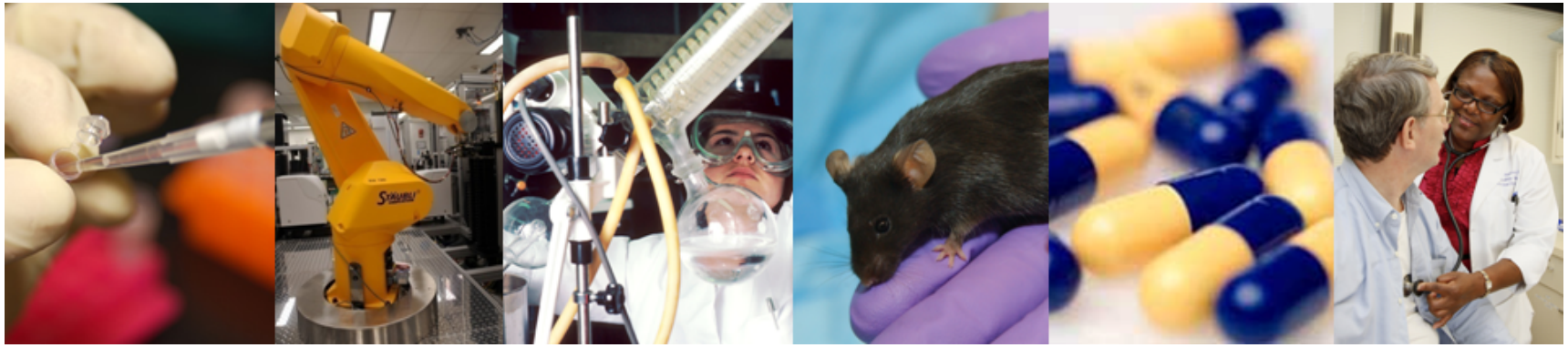


“Houston, we have a problem”

- Fundamental science unprecedentedly advanced, but:
  - » Poor transition of those advances to interventions that tangibly improve human health
  - » Drug/device development system in crisis
  - » Clinical trials system in crisis
  - » Poor adoption of demonstrably useful interventions

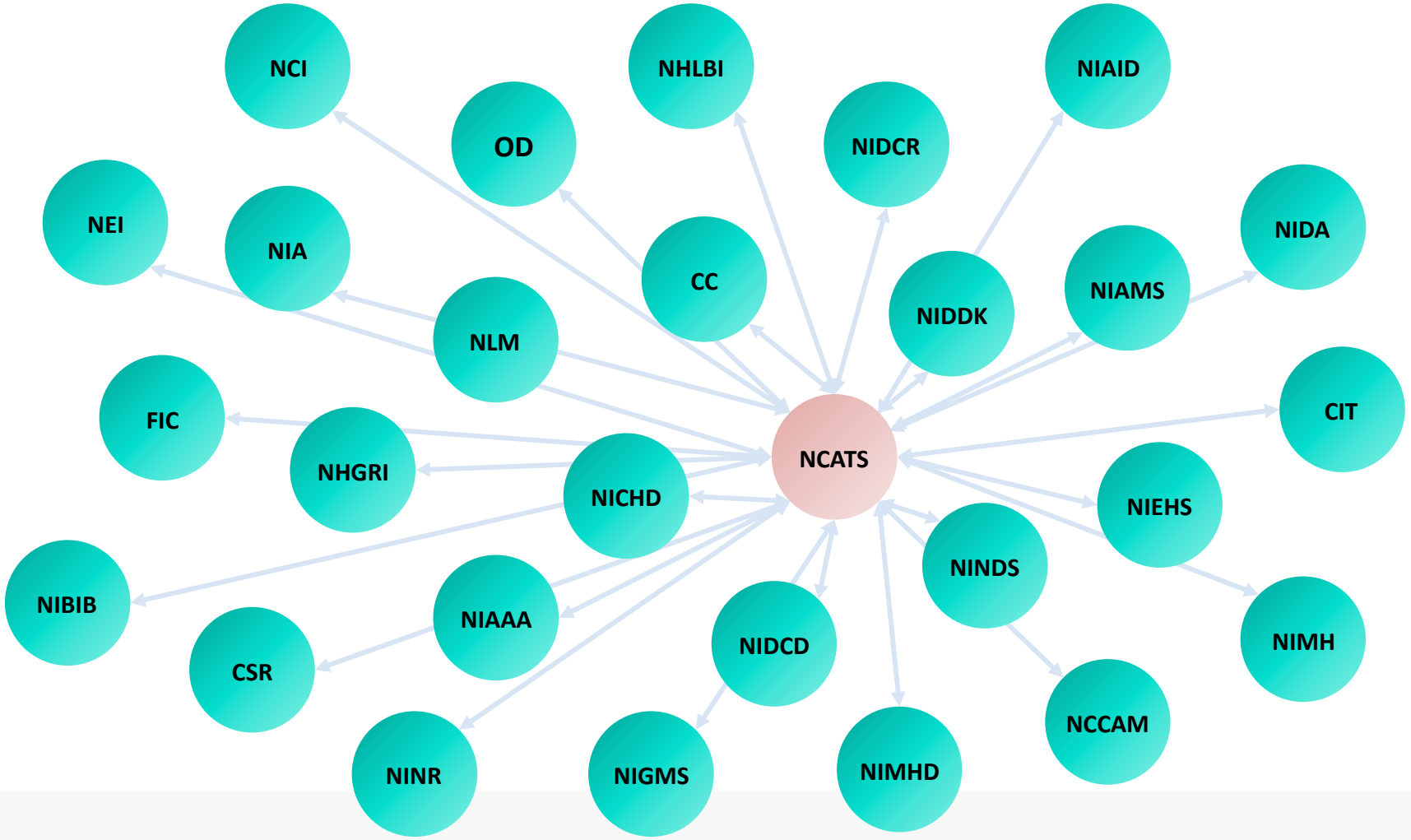
People unhealthier and funders of biomedical research enterprise (public and private) impatient

NCATS Mission

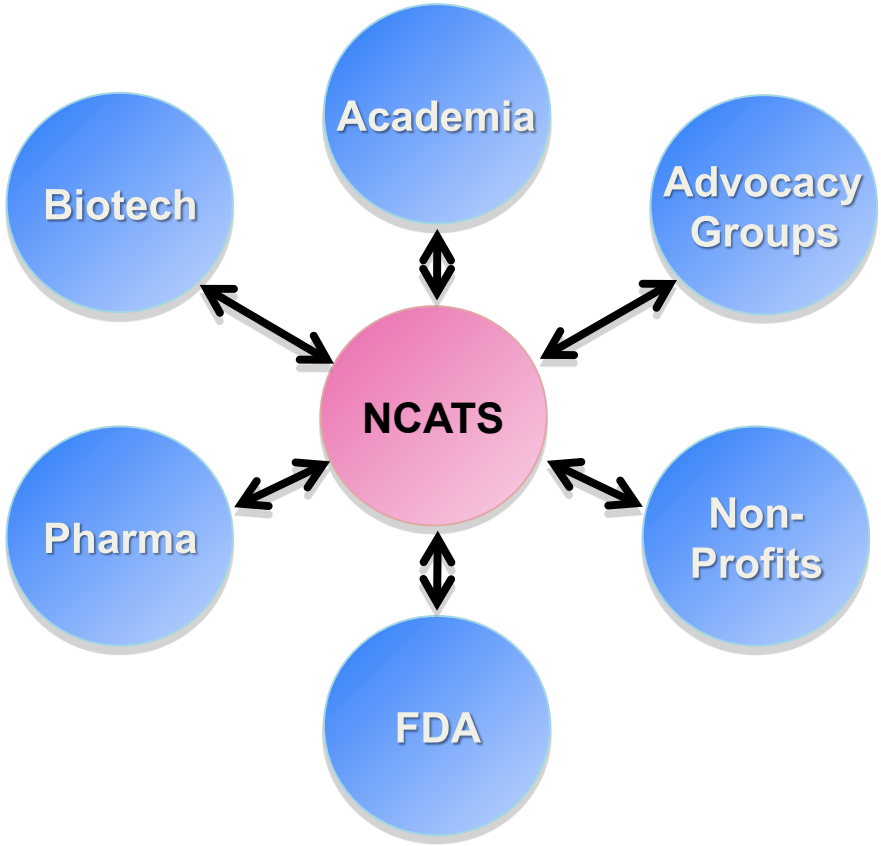


To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

Catalyzing Collaborations Within NIH

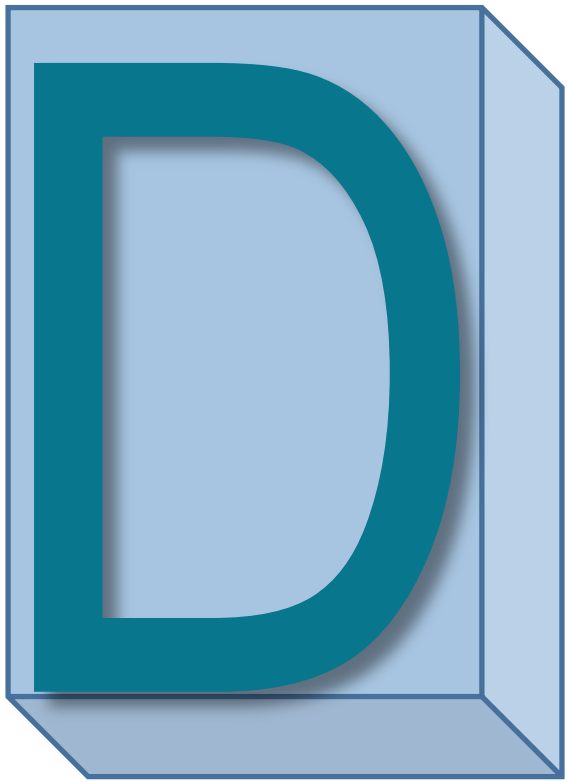


Catalyzing Collaborations Outside NIH



- Complements — does not compete — with the work of others
- Revolutionizes the process of translation by promoting innovative research
- Galvanizes and supports new partnerships
- Supports and augments regulatory science and its application
- Expands the precompetitive space

NCATS "3D's"



evelop

emonstrate

isseminate

Characteristics of NCATS Initiatives and Programs

- Address significant bottlenecks in the process of translation
- Highly collaborative across NIH, other government agencies, and with the private sector.
- Quick to respond to needs of biomedical researchers

Health Care and Education Reconciliation Act of 2010 (HCA)

- Life Science Provisions of the HCA Qualifying Therapeutic Discovery Project Credit (PPA §9023)
  - » Biologics Price Competition and Innovation Act (PPA §7002)
  - » Economic Provisions:
    - ○ Expansion of 340B Medicare Coverage (PPA §7101-03)
    - ○ Filling the Donut Hole in the Part D Drug Benefit (PPA §7101-03; HCA §1101)
    - ○ Medical Device Tax (PPA §9009; HCA §1191)
    - ○ Increase in Medicaid Rebate (PPA §3202; HCA §1102(d))
    - ○ Branded Drug Manufacturer Fee to Fund HealthCare Reform (PPA § 9008; HCA §1404)
  - » Entities Established:
    - ○ Patient Centered Outcomes Research Institute
    - ○ Independent Medicare Advisory Board (PPA §10320)
    - ○ Cures Acceleration Network (PPA §10409)

Cures Acceleration Network

- Promote innovation in technologies to support advanced research and development and production of High-Need Cures
- Accelerate the development of High-Need Cures utilizing medical products, behavior therapies, or biomarkers
- Assist recipients of CAN awards with establishing protocols that comply with the Food and Drug Administration standards throughout all stages of the development of a medical product

"High-Need Cures" definition: drug, biological product, or device that, in the determination of the NCATS Director is a priority to diagnose, mitigate, prevent or treat harm from any disease or condition; and for which the incentives of the commercial market are unlikely to result in its adequate or timely development.

Tissue Chip for Drug Screening: Microsystems Initiative

- Aims to develop tissue chips that mimic human physiology to screen for safe, effective drugs using best ideas in engineering, biology, toxicology
- NIH Investment (Funded Through CAN + Common Fund) = $70M/5 years
- DARPA Investment = $75M/5 years
- FDA Investment = Regulatory and toxicology expertise
- NCATS and DARPA independently manage and fund separate but highly coordinated programs

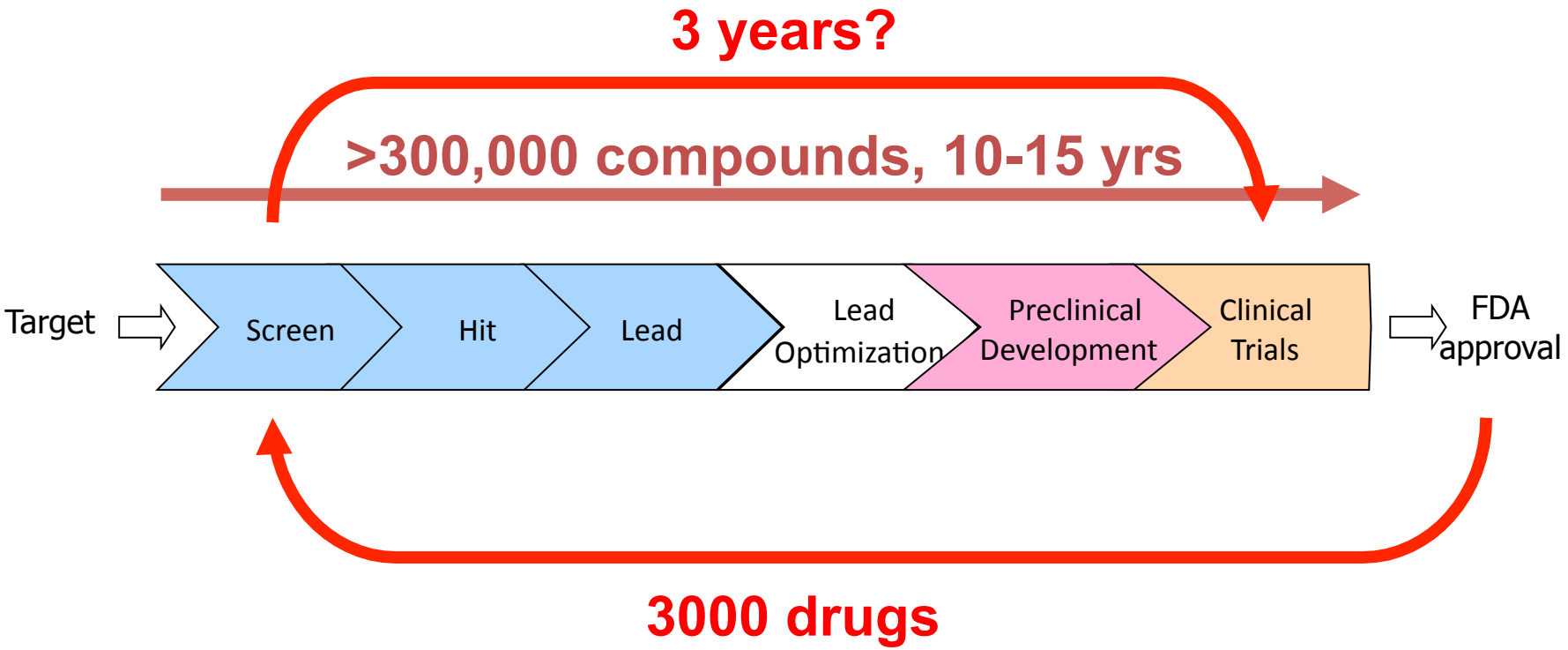
NIH National Institutes of Health
Turning Discovery Into Health

DARPA

FDA

NIH
National Center for Advancing Translational Sciences

Two approaches to therapeutics for rare and neglected diseases

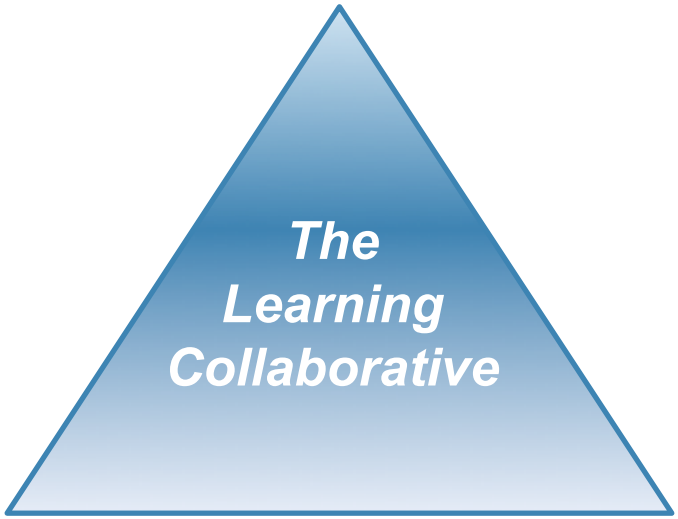


Repurposing Approved Drugs

Auranofin – Rapid translation through collaboration for CLL

NIH National Center for Advancing Translational Sciences

- Industrial scale HTS, medicinal chemistry, and bioinformatics capabilities
- Recruited pharma experience



KU THE UNIVERSITY OF KANSAS
The Institute for Advancing Medical Innovation

- CTSA institution
- Bench to bedside translation in drug repurposing
- Recruited pharma experience

LEUKEMIA & LYMPHOMA SOCIETY
fighting blood cancers

- $60M invested annually in basic blood cancer research
- Therapy Acceleration Program home to 60 active projects
- World wide network of blood cancer experts

Repurposing Approved Drugs

HPbCD – Formulating a treatment for Niemann-Pick Type C (NPC)

- Autosomal recessive neurodegenerative disorder characterized by neurovisceral lipid storage
- Incidence: 1/120,000
- No FDA-approved therapy
- TRND pilot project: repurposing an agent that can clear cholesterol from NPC patient-derived cells

Collaborators
- NIH (NICHD, NHGRI)
- Washington University (Biochemistry)
- Albert Einstein and UPenn (Animal models)
- Johnson &Johnson Pharmaceuticals

NPC disease foundations involved and facilitating

TRND project milestones
- ✓ Proof-of-concept in animals
- ✓ Biomarker development
- ✓ Bio-analytical method development
- ✓ PK/PD, toxicology studies
- ✓ IND filing

Proof-of-concept clinical trial

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Center for Advancing Translational Sciences (NCATS)

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

For Immediate Release
Wednesday, January 23, 2013

Contact:
NCATS Office of Communications
301-435-0888

NICHD Press Office
301-496-5133

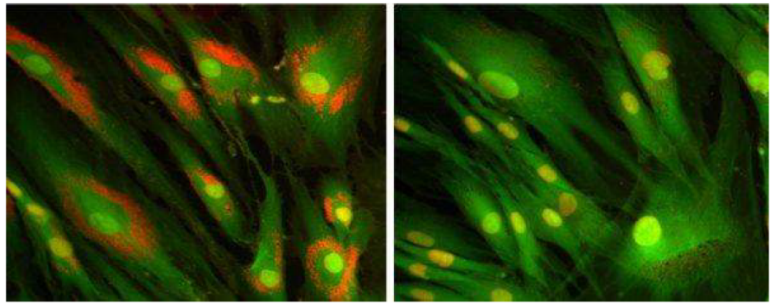
"The NIH cyclodextrin trial has started and the first patient will receive the drug on Monday 2/4. We are very excited to get started and to get data that will direct future studies of cyclodextrin in NPC. We have been in contact with many families and would like to provide an update about the trial screening process.

NIH clinical trial begins for treatment of rare, fatal neurological dis

Government, industry, academia, and patient groups collaborate on Niemann

A clinical trial to evaluate a drug candidate called cyclodextrin as a possible tre
C1 (NPC), a rare and fatal genetic disease, will start today, researchers annou
Center for Advancing Translational Sciences (NCATS) and the *Eunice Kennec*
Health and Human Development (NICHD) will conduct the clinical trial at the NIH Clinical Center. Reaching this trial stage required collaboration among government, industry, patient advocacy groups and academic researchers.

No therapies approved by the U.S Food and Drug Administration are available to treat NPC. The disease is characterized by the inability of cells to metabolize and dispose of cholesterol and lipids. It causes excessive amounts of cholesterol to accumulate within the liver, spleen and brain. NPC leads to progressive impairment of motor and intellectual function in early childhood. In childhood onset cases, life expectancy does not normally exceed a patient's teenage years.



At left, fibroblasts homozygous for mutations in NPC1 demonstrate and increased accumulation of red Lysotracker staining indicative of the storage disease. At right, addition of cyclodextran rescues this lysosomal storage defect.

"A crucial part of the NCATS mission is to collaborate within and beyond the NIH on projects to improve and accelerate the translational research process and deliver tangible improvements in human health," said NCATS Director Christopher P. Austin, M.D. "The cyclodextrin project is an important step in the development of both a potential treatment for a devastating disease that ravages the bodies and minds of its victims and a more efficient way to do translational projects."

NIH-Industry Pilot Program

Discovering New Therapeutic Uses for Existing Molecules

Goal: To identify new therapeutic uses of proprietary compounds and biologics across a broad range of human diseases in areas of medical need.

- Match candidate agents made available by 8 pharmaceutical partners with innovative ideas for new indications from the biomedical research community
- Criteria for agents included in pilot include: prior human studies, well-characterized mechanism of action, safety profile understood, company's commitment to supplying material and expertise
- NIH Cooperative Agreements "U" Awards: Awardee has primary responsibility for the project, NCATS will remain involved during execution, steering committee oversight

NIH-Industry Pilot Program

Discovering New Therapeutic Uses for Existing Molecules

Table of Compounds and Biologics*

Pfizer Inc.	PF-05416266 (senicapoc; ICA-17043)
Mechanism of Action	Calcium-activated potassium channel blocker (KCa3.1), intermediate-conductance http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=384 http://www.ncbi.nlm.nih.gov/gene/3783
Overview	Senicapoc is a potent and selective blocker of the human KCa3.1 channel. Potency: IC_{50} = 6.2 nM for K^+ current through human KCa3.1 expressed in CHO cells or native KCa3.1 in human lung mast cells; 11 nM through Gardos channels in human red blood cells (RBCs); and 20 nM for increase hemoglobin concentrations in human RBCs. Selectivity: IC_{50} > 1 uM for Kv1.5, hERG, Na (TTX sensitive), IKs, KvLQT, and h-H1.
Safety/Tolerability	Senicapoc was safe and generally well tolerated at 10 mg QD for 52+ weeks (mean plasma concentration ~100 ng/ml). Non-sickle cell crisis-related adverse events (Aes) that occurred in ≥ 5% of subjects, and more often in senicapoc treated, included urinary tract infection, nausea, arthralgia, pain in extremity, and cough. Nonclinical toxicology data support clinical studies up to at least 1 year in duration and include genetic, reproduction, and carcinogenicity studies.
Additional Information	Senicapoc has a mean human plasma half-life of 12.8 days, so a loading dose followed by daily maintenance doses provide near constant plasma concentrations. Pharmacodynamic (PD) evidence of channel block was demonstrated in humans by increases in hemoglobin and decreases in indicators of hemolysis [lactate dehydrogenase (LDH), reticulocyte count and indirect bilirubin]. E_{MAX} model fitting revealed 50% maximal inhibition of the Gardos channel at a plasma concentration of 54 ± 8 ng/ml. Senicapoc is a modest inducer of CYP3A4 with no or minimal effect on 7 other human CYP450 enzymes.
Suitable for and Exclusions	There are no known contraindications for senicapoc. One pharmacokinetic (PK) and PD study has been performed in pediatric subjects (6 – 15 years of age). No study has included subjects > 65 years old.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=PF-05416266+OR+senicapoc+OR+ICA-17043
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=senicapoc%20OR%20ICA-17043 http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08520.x/pdf

Code Number & Link to More Information	Mechanism of Action	Original Development Indication(s)	Route of Administration Formulation Available (CNS Penetrant+)
			Oral
			Oral
			Oral
			Oral (Yes)
			Oral (Yes)
			Oral (Yes)
			Oral
			Oral
			Oral
	receptor 2 (CCR2) antagonist		Oral (No)
CE-326597	Cholecystokinin 1 receptor (CCK-1R) (or CCK_A receptor) agonist	Obesity in type II diabetes	Oral

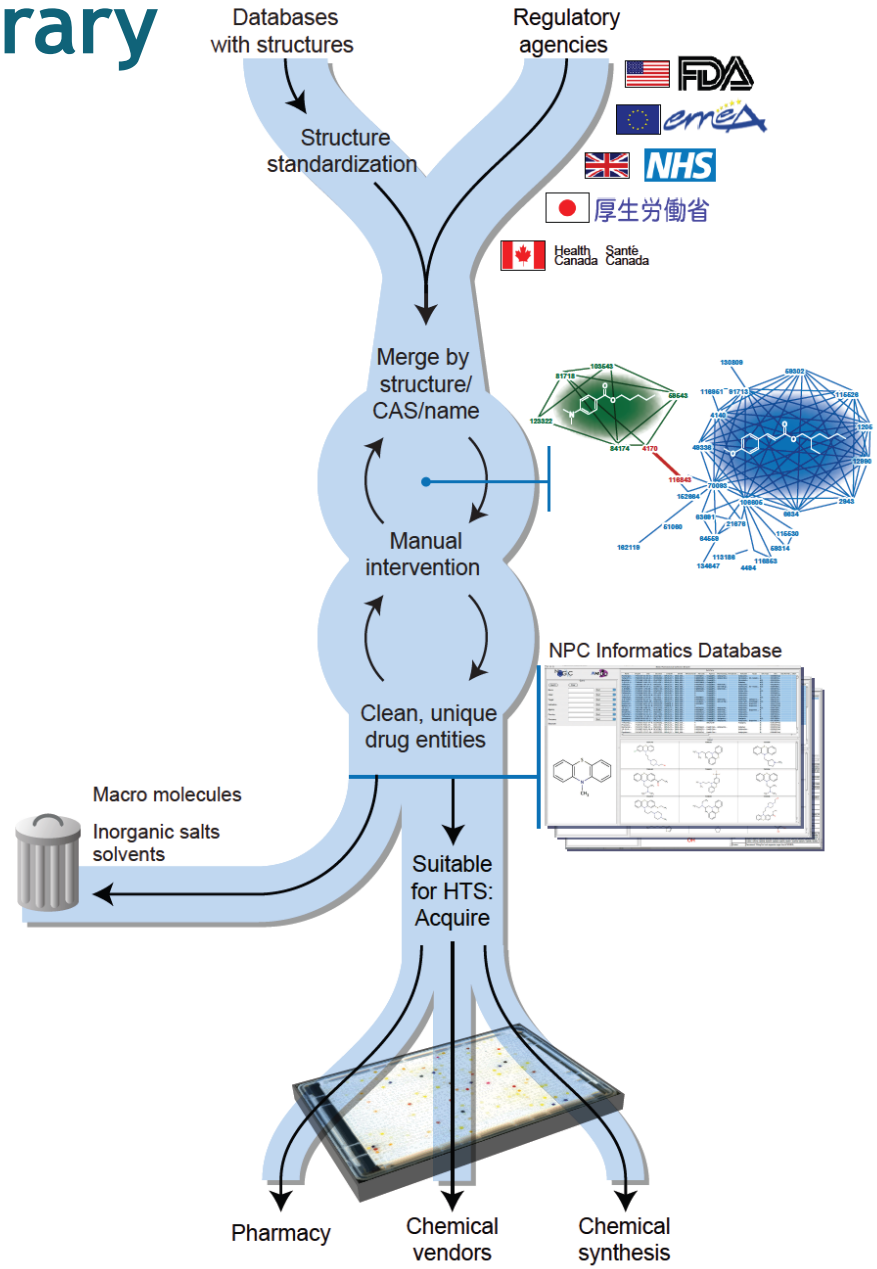
National Center for Advancing Translational Sciences

Procuring an HTS Library for Repurposing

Currently, many important advances in the development of new assays that capture on a cellular level relevant disease-causing defects

- Patient-derived iPSCs
- High-content screening

Procure, for *in vitro* testing, a complete collection of approved substances for HTS assay



NIH National Center for Advancing Translational Sciences

NCATS Pharmaceutical Collection

Drug Source	In house	In procurement	Total
US FDA	1676	141	1817
UK/EU/Canada/Japan	807	126	933
Total Approved	2391	359	2750
INN	929	3952	4881
Total	3319	4312	7631

Informatics sources for NPC

- US FDA: Orange Book, OTC, NDC, Green Book, Drugs@FDA
- Britain NHS
- EMA
- Health Canada
- Japan NHI

Physical sources for NPC

- Procurement from >70 suppliers worldwide
- In-house purification of APIs from marketed forms
- Custom synthesis

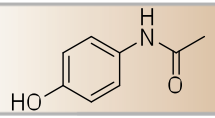
How Many Drugs Are There?

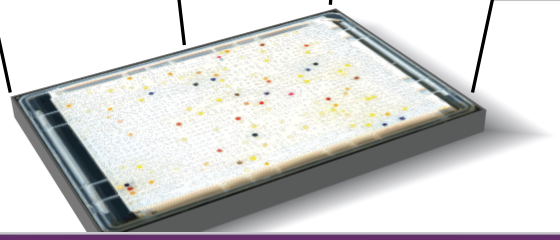
Term	FDA	Worldwide	
Drug Product	>140,000		Product with defined package size, dose, formulation of API(s)
Drug	>19,000	>25,000	Brand or generic name of approved product that defines API(s)
API	4,695	7,980	Physical substance intended to be used in manufacture of drug product
Active Moiety	2,794	4,374	Chemical moiety excluding salts, esters, etc. responsible for pharmacological activity
HTS Suitable	1,817	2,750	Chemical entity of defined structure amenable to high-throughput screening

Tylenol 8 Hour, Dayquil Sinus NyQuil Cough, Infants' Tylenol

Tylenol, Acetominophen, Panadol, Datril, Paracetamol

103-90-2

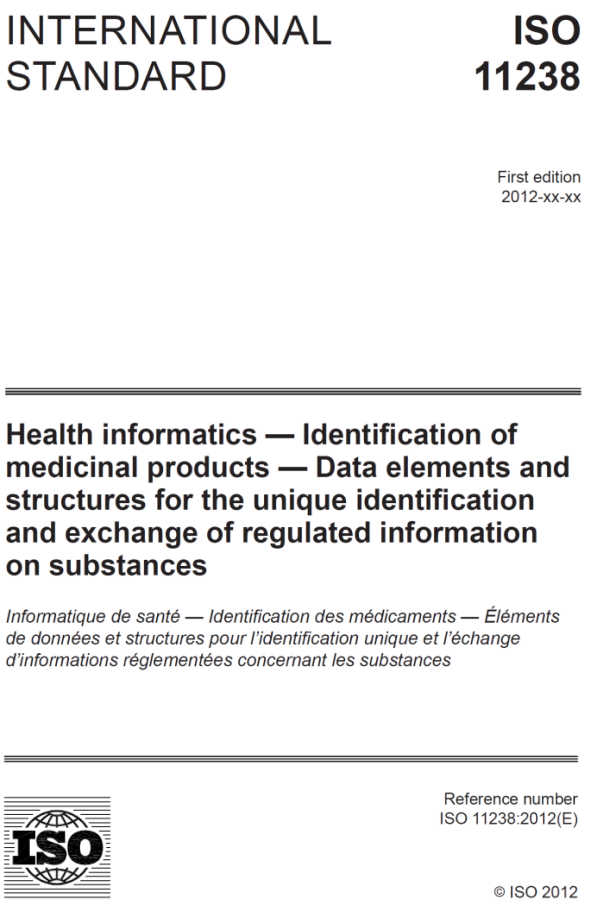




Registration of Substances and Related Information Based on ISO 11238

Scope

This International Standard provides an information model to define and identify substances within medicinal products or substances used for medicinal purposes, including dietary supplements, foods and cosmetics.



INTERNATIONAL STANDARD

ISO 11238

First edition
2012-xx-xx

Health informatics — Identification of medicinal products — Data elements and structures for the unique identification and exchange of regulated information on substances

Informatique de santé — Identification des médicaments — Éléments de données et structures pour l'identification unique et l'échange d'informations réglementées concernant les substances

Reference number
ISO 11238:2012(E)

Learn More About NCATS

ncats.nih.gov

- **Questions:** info@ncats.nih.gov
- **Like us on Facebook:** facebook.com/ncats.nih.gov
- **Follow us on Twitter:** twitter.com/ncats_nih_gov
- **Join our listserv, and subscribe to our e-newsletter via links at:** www.ncats.nih.gov/news-and-events/e-news/e-news.html